



Brief Report

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Dendrobium Nobile Stem Extracts May Prevent Cancer by Inhibiting Cytochrome P450 1A1 and 1B1

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Abstract

Traditional Chinese medicine has used herbs for many centuries to treat a variety of ailments including cancer. Discovering the active components in many of these herbs has been a line of research for a number of scientific investigations. Two compounds extracted from dendrobium nobile stems have previously demonstrated anticancer activity by inducing apoptosis in various cancer cell lines. We have found that extracts from the stem of dendrobium nobile inhibit cytochrome P450 1A1 and 1B1. Dendrobium nobile stems extracted in dimethylsulfoxide, dimethylformamide, or ethanol inhibited cytochrome P450 1A1 and 1B1 to 41% or less of their uninhibited activity. Specifically, the ethanol extracts provided the greatest inhibitory effects with an IC_{50} of 0.63 μ M with respect to cytochrome P450 1A1 and an IC_{50} of 1.4 μ M with respect to cytochrome P450 1B1. These results suggest that these extracts contain compounds that could prevent or treat cancer by a different mechanism from ones previously discovered and could lead to the identification of new chemopreventive compounds from the stems of dendrobium nobile.

Keywords: Cytochrome P450 1A1; 1B1; CYP1A1; CYP1B1 chemo preventive; Dendrobium nobile stem; IC_{50} ; Natural products; Biochemistry herbal medicine

Introduction

It is estimated that there will be 2,001,140 new cancer cases and 611,720 cancer deaths in the United States in 2024 based on statistical modeling by Siegel et al. [1], making cancer the second leading cause of death nationwide. Because cancer is so prevalent in the United States, billions of federal dollars are spent each year to find appropriate ways to prevent and treat this disease (www.cancer.gov) [2]. While the 5-year survival rate for all cancers has increased from 49% in the mid-1970s to 69% in the mid-2010s because of better screening and early detection of cancers and improved treatments, many scientists are committed to increasing this survival rate, and simultaneously

reducing the mortality rate from the disease [1].

Increasingly, scientists are investigating natural products, particularly from plants, as a source for finding chemopreventive or chemotherapy agents. It is estimated that up to 50% of all anti-tumor agents are natural products [3]. Yet, it is also estimated that less than 1% of the 250,000 to 350,000 plant species have been screened for any pharmacological activity [4]. Thus, there is a vast pool of living species that we have not investigated from which we can find novel natural products to prevent and treat a variety of diseases including cancer. In addition, because many cancers arise out of multiple abnormal signal transduction or other pathways, combinatorial therapy can be more effective than monotherapy [3-8]. Typically, monotherapy targets one pathway and it is subject to being partially effective and also to becoming ineffective because of drug resistance. Combinatorial therapy can overcome the drawbacks of monotherapy including targeting multiple pathways involved in suppressing cell proliferation, interfering with tumor signaling pathways, and in stimulating DNA repair mechanisms in healthy cells while stimulating apoptosis or other means of cell death in tumor cells [3]. This therapy can also help overcome issues of poor bioavailability [5] and of drug resistance [3] associated with using one compound by providing multiple targets and the potential for synergistic effects with multiple compounds [5,8]. Finally, by finding many more compounds to treat cancer, this can hopefully lead to finding effective combinations of drugs that can reduce one of the drawbacks of combinatorial therapy, which is herb-drug or drug-drug interactions involving prescription medications [3,9,10]. In such cases herbal extracts may lower the concentration of drugs in the bloodstream and thus reduce the drug's effectiveness, or increase the concentration of prescription medications such that they could become toxic to the patient [11].

One source of natural products is from herbal medicines that have been used for centuries in China, India, and other Asian countries to treat a variety of ailments [12,13]. In traditional Chinese medicine (TCM), herbs from many different plant species have been used as analgesics, anti-inflammatory agents, antioxidants along with many other bioactivities to treat many human disorders including cancer [12-17]. In particular the stems from Dendrobium nobile (D. nobile stem) contain many compounds such as polysaccharides, alkaloids, flavonoids, and others that have been used to prevent and treat many different ailments. These compounds have anti-inflammatory, antifungal, antiallergic, antioxidant, and antiplatelet aggregation activities, to name a few, that have been used to prevent and treat diabetes, hypertension, and protect against neurodegeneration [18-21]. Two compounds isolated from D. nobile stem have anticancer activity: denbinobin and nudol. Denbinobin inhibits SNU-484 human gastric cancer cells [22], A549 lung adenocarcinoma cells [23,24], and several other cancer cell lines [24]. On the other hand, nudol is active against osteosarcoma U2OS cells [20]. Both compounds can exert their anticancer effects by inducing apoptosis in at least some of these cell lines: denbinobin in A548 adenocarcinoma cells [23], and nudol in U2OS osteosarcoma cells [20].

It is possible that Chinese herbs contain other types of compounds that have anticancer or chemopreventive ability, and identifying these compounds will be important in expanding the possible options for

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combinatorial therapy for cancer. Compounds such as resveratrol and other stilbenes have shown potent chemopreventive and anticancer ability towards a variety of cancers or cancer cell lines including HL60 [25,26] and K562 [27] leukemia cell lines, colon cancer in male Wistar [28,29] and male Fisher [29,30] rats, and MCF-7 breast cancer cells [31]. Because resveratrol and other stilbenes inhibit cytochrome P450 1A1 and 1B1 as the potential mechanism by which they exert their antimutagenesis and chemopreventive effects [32-38], we decided to test whether various Chinese herb extracts inhibit cytochrome P450 1A1 and 1B1. If these extracts inhibit one or both of these enzymes, it could lead to identifying novel compounds present in Chinese herbs that have anticancer activity, or identify a new mechanism by which a known anticancer compound in these herbs prevents and/or treats cancer.

Our studies have demonstrated that extracts from the stems of Dendrobium Nobile (D. nobile stem) inhibit cytochrome P450 1A1 and 1B1 at levels far lower than from other species of chinese herbs tested in this laboratory. Thus, D. nobile stem extract is a promising source for finding new compounds that have anticancer and/or chemopreventive activity, or identifying a new mechanism by which a known anticancer compound exerts its effects.

Materials and Methods

Solvent Extraction

Each herb sample was subdivided into different samples, and each subdivided herb sample was extracted in one of five different solvents: cyclohexane, ethanol, DMSO, DMF, and boiled water. First, 2.0 g of each herb sample was grounded up in a mortar and pestle. The herbs were then placed in separate closed containers and submerged in the

appropriate solvent. The herbs soaked for one week in the solvent while being stirred once a day. Gravity filtration was used to separate the herbs from extracted solution, and the solutions were then dried in a fumigation hood. Once dried, the extracts were weighed and then dissolved in spectroscopic grade DMSO to a concentration of 1.0 mg of extract/mL.

Cytochrome P450 1A1 and 1B1 assays

Cytochrome P450 1A1 and 1B1 assays were modified from those described by Chun et al. [39] Assays were run in triplicates in the absence of inhibitor and in the presence of inhibitor at each inhibitor concentration. Each reaction consisted of 0.10 M phosphate buffer pH 7.4, 5.0 μM ethoxyresorufin (ER), 6.25 mM MgCl₂, 7.1 mM EDTA, 28.0 μM NADPH, and either 10 nM CYP1A1 or 5 nM CYP1B1. NADPH was added to initiate the reaction at 37°C. The reaction was stopped at 2 minutes by adding 2.0 mL of chilled methanol. The test tubes were then centrifuged for 25 minutes at 500 x g to remove the precipitate from solution. The resorufin product was then excited at 574 nm and the emission was read at 586 nm using a Fluoromax-4 spectrofluorometer. Decreasing amounts of resorufin fluorescence corresponded with decreased enzyme activity and thus increased enzyme inhibition.

Results and Discussion

The herb extracts were screened for their ability to inhibit Cytochrome P450 1A1 and 1B1 at a concentration of 10.0 μg/mL. Most herb extracts demonstrated little to no inhibition of the enzymes at this concentration having greater than 50% of the uninhibited enzyme activity (Table 1), and they included extracts from S. Adoxoides, A. Julibrissin bark, P. Notoginseng root, L. Japonicum spore, P. Vulgaris

Table 1: Screening values and IC₅₀ values for herb extracts with CYP1A1 and CYP1B1.

Herb	Solvent	1A1 Screen Percent of Uninhibited Enzyme Activity	1A1 IC ₅₀ μM	1B1 Screen Percent of Uninhibited Enzyme Activity	1B1 IC ₅₀ μM
D. Nobile Stem	DMSO	41	9.3	36	5.5
	DMF	35	6.2	21	3.4
	Ethanol	8	0.63	12	1.4
	Cyclohexane	86	ND ^a	44	ND ^a
	Water distillation	87	ND ^a	62	ND ^a
L. Japonicum Spore	DMSO	85	ND ^a	61	ND ^a
	DMF	87	ND ^a	42	ND ^a
	Ethanol	88	ND ^a	58	ND ^a
	Cyclohexane	97	ND ^a	77	ND ^a
	Water distillation	100	ND ^a	100	ND ^a
S. Adoxoides	DMSO	95	ND ^a	81	ND ^a
	DMF	88	ND ^a	85	ND ^a
	Ethanol	67	ND ^a	85	ND ^a
A. Julibrissin Bark	DMSO	95	ND ^a	93	ND ^a
	DMF	84	ND ^a	67	ND ^a
	Ethanol	59	ND ^a	58	ND ^a
P. Notoginseng Root	DMSO	76	ND ^a	96	ND ^a
	DMF	70	ND ^a	75	ND ^a
	Ethanol	75	ND ^a	83	ND ^a
P. Vulgaris Flower	DMSO	69	ND ^a	78	ND ^a
	DMF	76	ND ^a	61	ND ^a
	Ethanol	89	ND ^a	68	ND ^a
L. Ruthenicum	DMSO	93	ND ^a	90	ND ^a
	DMF	77	ND ^a	58	ND ^a
	Ethanol	92	ND ^a	77	ND ^a

^aND means not determined.

flower, and *L. Ruthenicum*. For example, the DMSO extract from *S. Adoxoides* inhibited CYP1A1 and CYP1B1 to 95% and 81% of the uninhibited enzyme activity respectively. The ethanol extract from *L. Ruthenicum* inhibited CYP1A1 and CYP1B1 to 92% and 77% of the uninhibited enzyme activity respectively. And, the DMF extract from *P. Notoginseng* root inhibited CYP1A1 and CYP1B1 to 70% and 75% of the uninhibited enzyme activity respectively.

However, several solvent extracts from *D. Nobile* stem did inhibit these two enzymes to 41% or less of the uninhibited enzyme activity (Table 1). This included the DMSO, DMF, and Ethanol extracts. The ethanol extract inhibited both CYP1A1 and CYP 1B1 the strongest with 8% and 12% of the uninhibited enzyme activity remaining for CYP 1A1 and CYP 1B1 respectively. The DMF extract left CYP 1A1 with 35% and CYP 1B1 with 21% of their full activity. Finally, the DMSO extract inhibited the enzymes more weakly leaving 41% and 36% of the uninhibited activity of CYP 1A1 and CYP 1B1 respectively. Other *D. Nobile* stem extracts had little to no inhibitory activity including those using cyclohexane and water indicating that the active components had solubilities favorable in the former solvents.

The *D. Nobile* stem extracts that inhibited CYP1A1 and CYP1B1 to 41% or less of the uninhibited enzyme activity were further studied to determine the IC_{50} concentration. Unsurprisingly, the ethanol extracts had the lowest IC_{50} values at 0.63 $\mu\text{g/mL}$ against CYP 1A1 and 1.4 $\mu\text{g/mL}$ against CYP 1B1. The DMF extract inhibited CYP 1A1 with an IC_{50} of 6.2 $\mu\text{g/mL}$ and inhibited CYP 1B1 with an IC_{50} of 3.4 $\mu\text{g/mL}$. Finally, the DMSO extracts had IC_{50} values of 9.3 $\mu\text{g/mL}$ against CYP 1A1 and an IC_{50} of 5.5 $\mu\text{g/mL}$ against CYP 1B1.

These data indicate that the stems of *D. nobile* contain compounds capable of inhibiting CYP1A1 and CYP1B1. As previously mentioned, resveratrol and other stilbenes have been shown to inhibit CYP1A1 and CYP1B1, and to reduce the size of tumors in some animal species and to induce apoptosis in various cancer cell lines. Thus, it is reasonable to speculate that *D. nobile* stem contains one or more compounds, beyond those already discovered, that may also have chemopreventive activity.

Furthermore, because several of the *D nobile* stem extracts inhibit CYP1A1 and CYP1B1, one would also know one mechanism by which the unidentified compounds in the *D. nobile* stem extracts could prevent cancer. CYP1A1 and CYP1B1 are important in converting a variety of compounds such as polycyclic aromatic hydrocarbons (PAHs) found in soot, automobile exhaust, charred meat cooked over an open flame, cigarette smoke, fossil fuel processing, etc. [40-42] into carcinogenic compounds that can react with a human's DNA [41,43]. The procarcinogenic PAHs are oxidized by CYP1A1 and CYP1B1 to epoxides, which are converted to diols by epoxide hydroxylase, and finally CYP1A1 and CYP1B1 will transform the diols to epoxydiols [44,45]. The epoxydiols can react with the amine groups in adenine and guanine residues found in DNA, which results in errors during DNA replication [41,46,47]. If the resulting mutations are located in the transcribed region of a gene associated with a protein that controls cell division, this can lead to uncontrolled cell division, which may result in a tumor. Thus, inhibiting these enzymes would prevent the above pathway from occurring.

Many compounds other than stilbenes also inhibit these enzymes including flavonoids, coumarins, alkaloids, and naphthoquinones as some examples [48]. And specific types of compounds from the above compound families demonstrate chemopreventive activity including imperatorin and bergamottin, types of coumarins, and quercetin and

hesperidin, types of flavonoids [49]. Thus, the Chinese herb extracts may contain one of more compounds either from one or more of the above family of compounds, or from a new family of compounds yet to be identified. It will important, therefore, for further studies on the *D. nobile* stem extracts to identify the specific compound(s) in these extracts that inhibit CYP1A1 and CYP1B1. This will provide more compounds that can then be tested for chemopreventive activity and if positive for this, it will add more compound choices for combinatorial cancer therapy.

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